Before We Start

- Presentation available for download at the end
- Q&A Box on the right
- Poll questions at the end – Thank you!
- Post-test by March 29, 2017 (please use the same link you accessed the webinar with)
- Email questions or concerns: bsnyder@utah.gov

Disclosures

- The Western Multi-State Division is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.
- Participants must complete the pre-test, attend the entire live event, and complete the post-test with a score of 80% or greater to earn one contact hour.
- No conflicts of interest are involved in this series. This includes no content relevant to commercial interest and no presence of commercial support.

SGLT-2 Inhibitors for Type 2 Diabetes Mellitus: Protecting Kidneys and Heart

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UNIVERSITY OF UTAH
SCHOOL OF MEDICINE
INTERNAL MEDICINE • MOLECULAR MEDICINE
ENDOCRINOLOGY BIOCHEMISTRY

Outline

1. To learn how SGLT-2 controls renal glucose handling

2. To understand SGLT-2 Pharmacology

3. To review SGLT2 trials, including GLP-1 agonist and DDP4I comparisons

Outline

1. Case
2. Physiology of Renal Glucose Handling
3. SGLT-2 Pharmacology
4. Trials, including GLP-1 agonist and DDP4I comparisons
5. Speculation on Mechanisms
6. Back to case
7. Framework for polypharmacy

Case

A 62-year-old, white male truck driver with type 2 diabetes of 12 years duration complicated by non-proliferative retinopathy, and stage 3A CKD (eGFR 55 mL/min) is found to have a Hemoglobin A1c of 11.1%. He also has hypertension and mixed hyperlipidemia. He does not smoke tobacco. His 2013/16 ACC/AHA 10-year risk of an ASCVD event is 24.5%. BMI 34 kg/m^2.

His medications are:

- Aspirin 81 mg daily
- Atorvastatin 40 mg daily
- Chlorthalidone 25 mg daily
- Lisinopril 40 mg daily
- Metformin 1,000 mg twice daily- started 10 years ago
- Nifedipine extended release 60 mg daily

Case 1

He refuses to initiate insulin because this will jeopardize his commercial drivers' license.

He took pioglitazone and glimepiride for several years and does not want either again because of the weight gain and frequent hypoglycemia caused by these drugs, respectively.

Review of pharmacy records shows excellent adherence to his regimen (90 day supplies of each drug filled consistently).

Case 1

The patient agrees to begin exenatide 10 mcg bid, and after 4 months, the Hemoglobin A1c decreases to 9.2%. He also loses 7 kg and sees his home blood pressure readings decrease to an average of 130 mm Hg systolic. He checks his capillary blood glucose twice daily, and has an median morning value of 175 mg/dL and a bed-time median value of 210 mg/dL.

At a return visit he agrees to begin empagliflozin 12.5 mg bid in combination with metformin 1000 mg.

He is counseled about maintaining adequate fluid intake. He is also instructed to go to the emergency room if he develops dysuria and to inform the treating physician that he takes a drug that causes glycosuria.

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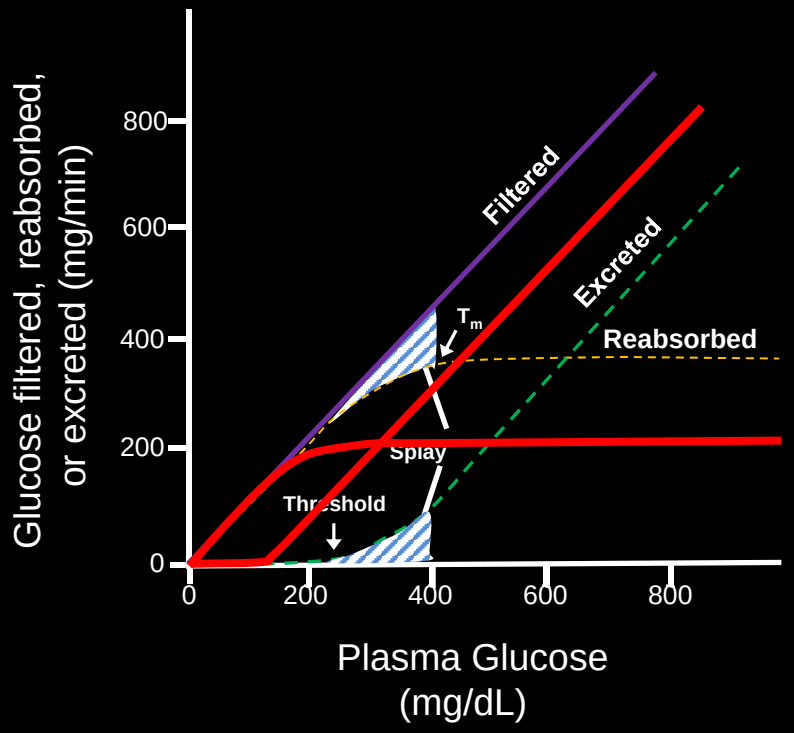
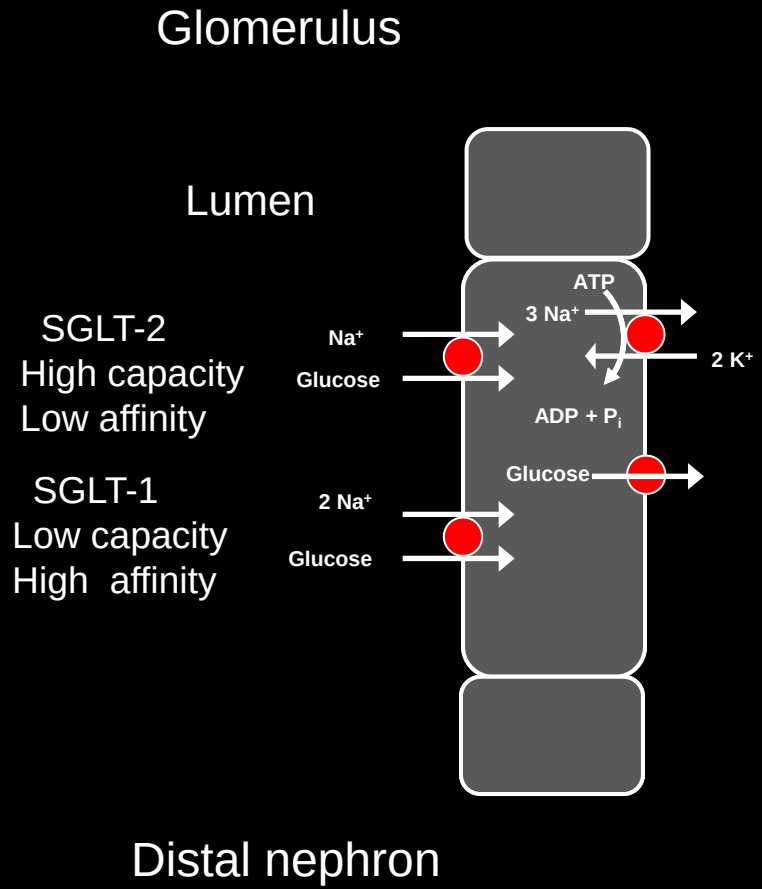
Proximal Tubular Physiology





Modified from Costanza 5th ed. (left); Vander's 6th ed. (right).

Phlor*h*izin

Josef von Mering, MD was the first to show that Phlorhizin causes glycosuria

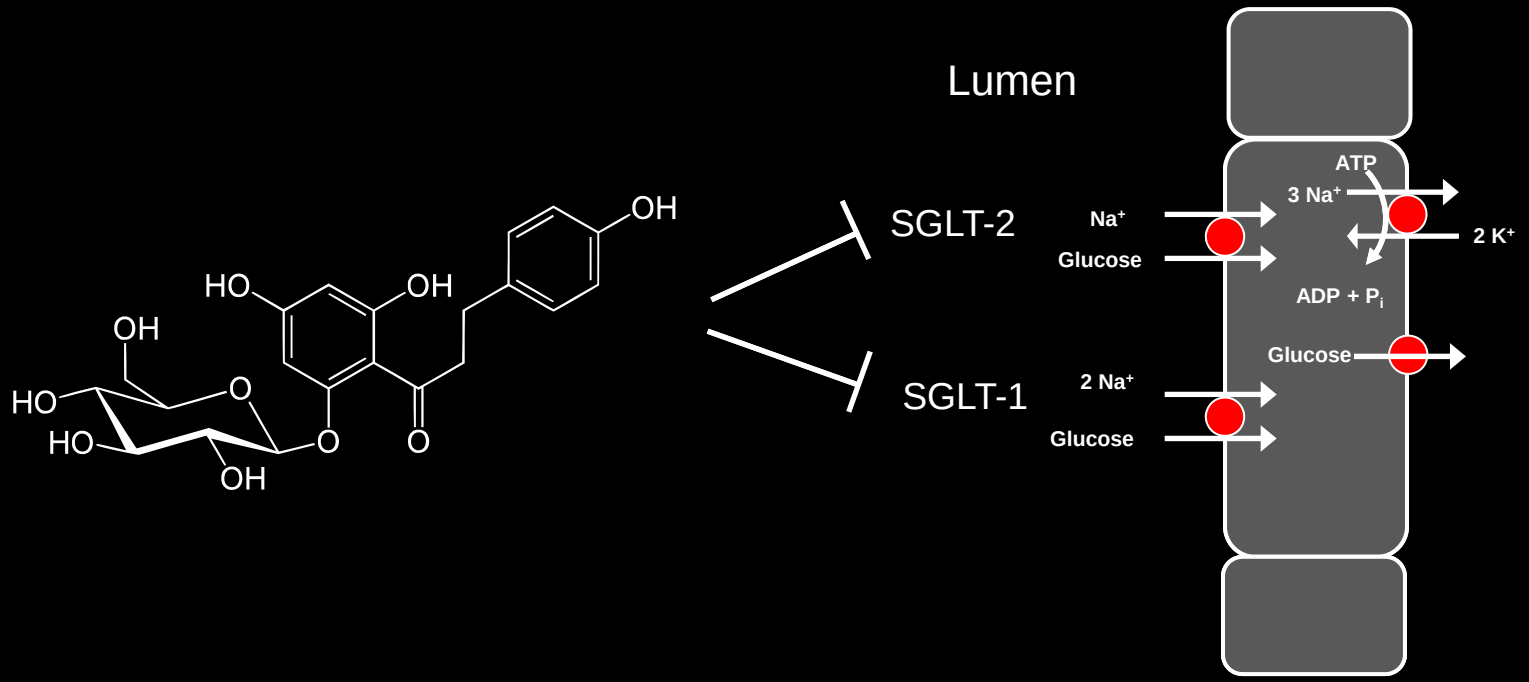
Naturally occuring 2-glucoside of phloretin found in the leaves, bark and seeds of:

- Apples
- Pears
- Cherries

[2] This word is also spelled phloridzin and phlorizin, which are incorrect (Külz und Wright, Zeitschrift für Biologie, 1890, xxvii, p. 181). Webster and the Century Dictionary give phlorizin, but the more correct spelling implied by the Greek derivative φλοιόῤῥιζος demands the use of phlorhizin.

Reilly, Nolan and Lusk 1989. Am J Physiol 1:395-410.

Phlorizin is a non-selective SGLT inhibitor



Poor oral bioavailability
Short half life
Intestinal angina from the delivery of glucose to the colonic flora

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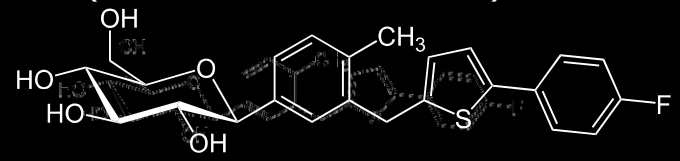
Gliflozins Are Selective SGLT2 Inhibitors

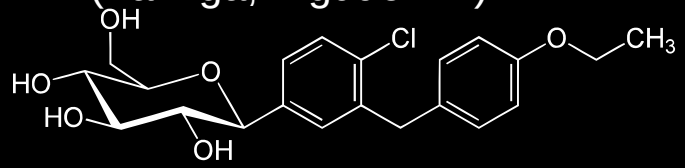
canagliflozin

(Invokana; Invokamet)



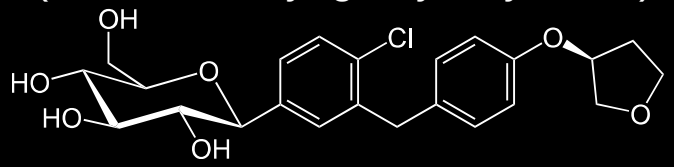
dapagliflozin

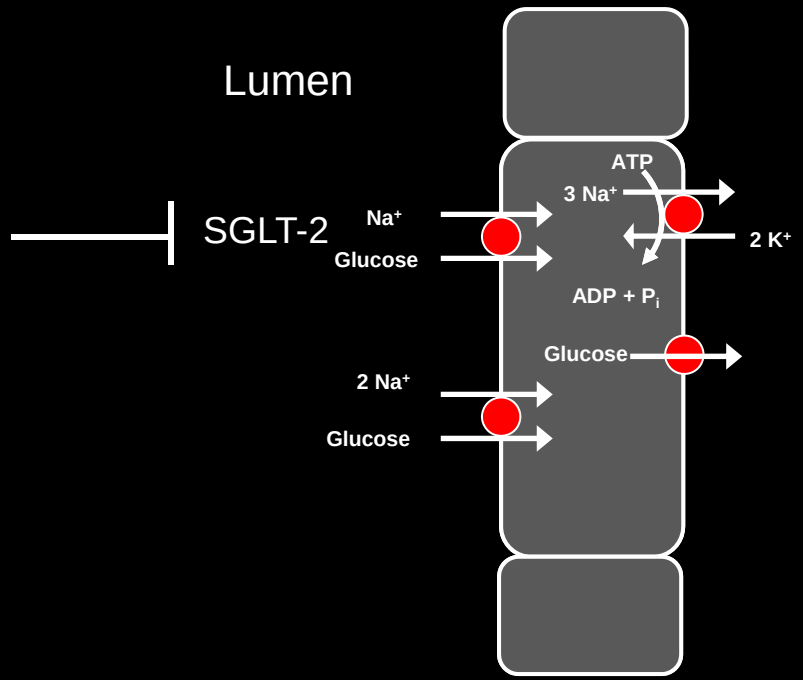
(Farxiga; Xigduo XR)



empagliflozin

(Jardiance; Syngardy; Glyxambi)





What We Know About SGLT2 Inhibitors

Good:

1. Weight loss (2 to 5 kg) – visceral and subcutaneous adipose (fat oxidative state)
2. Decrease in blood pressure: natriuresis and osmotic diuresis
3. Ketosis for optimal heart metabolism
4. Modest A1c reduction when added to metformin

Bad:

1. *Candida albicans* vulvovaginitis and *C. balanitis* in men
2. UTI, both sexes
3. Excessive ketoacidosis, with focus on acidemia
4. AKI from excessive osmotic diuresis (FDA warning for cana-)
5. Bone mineral loss (unclear mechanism; maybe no difference in fracture rate)
6. Bladder cancer (dapa-unclear mechanism; part of label)
7. Excess foot amputations (FDA warning for cana-)

Cost and Drug Interactions

Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Cost of 30-day supply	10 and 25 mg tablets; $411	100 and 300 mg tablets; $411	5 and 10 mg tablets; $412
Usual Dose	10 mg daily in the morning; may increase to 25 mg	100 mg daily before first meal; may increase to 300 mg once daily if eGFR >60	5 mg daily in the morning; may incrase to 10 mg
Drug Interactions	No significant clinical interactions noted.	Canagliflozin expoure is reduced with rifampin, phenytoin, phenobarbital, ritonavir. Consider using 300 mg dose.	No significant clinical interactions noted.

Ndefo et al. 2015. Empagliflozin (Jardiance): A Novel SGLT2 Inhibitor for the Treatment of Type-2 Diabetes. 40:364-8.

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FDA Guidance on Diabetes Drugs

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

For new clinical studies in the planning stage:

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

December 2008; US Department of Health and Human Services, FDA, CDER

EMPA-REG OUTCOME Mortality Study

Criteria

18 years and over
EGFR >30 ml/min/1.73m^2
BMI 45 kg/m^2 or less
Known CAD, CVA or PVD

A1c between 7 and 9%, with washout of all diabetes medications prior to start.

Primary Outcome

death from CV causes, non-fatal MI, or non-fatal stroke.

Secondary Outcome

Primary + hospitalization for unstable angina.

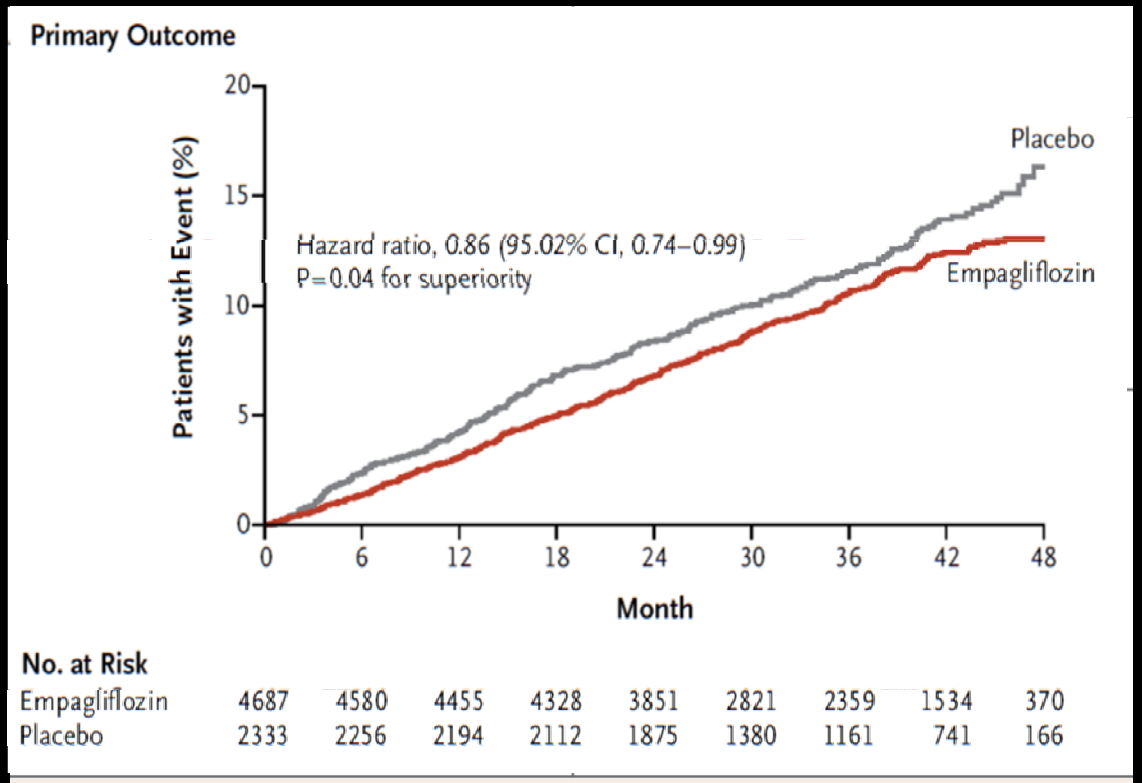
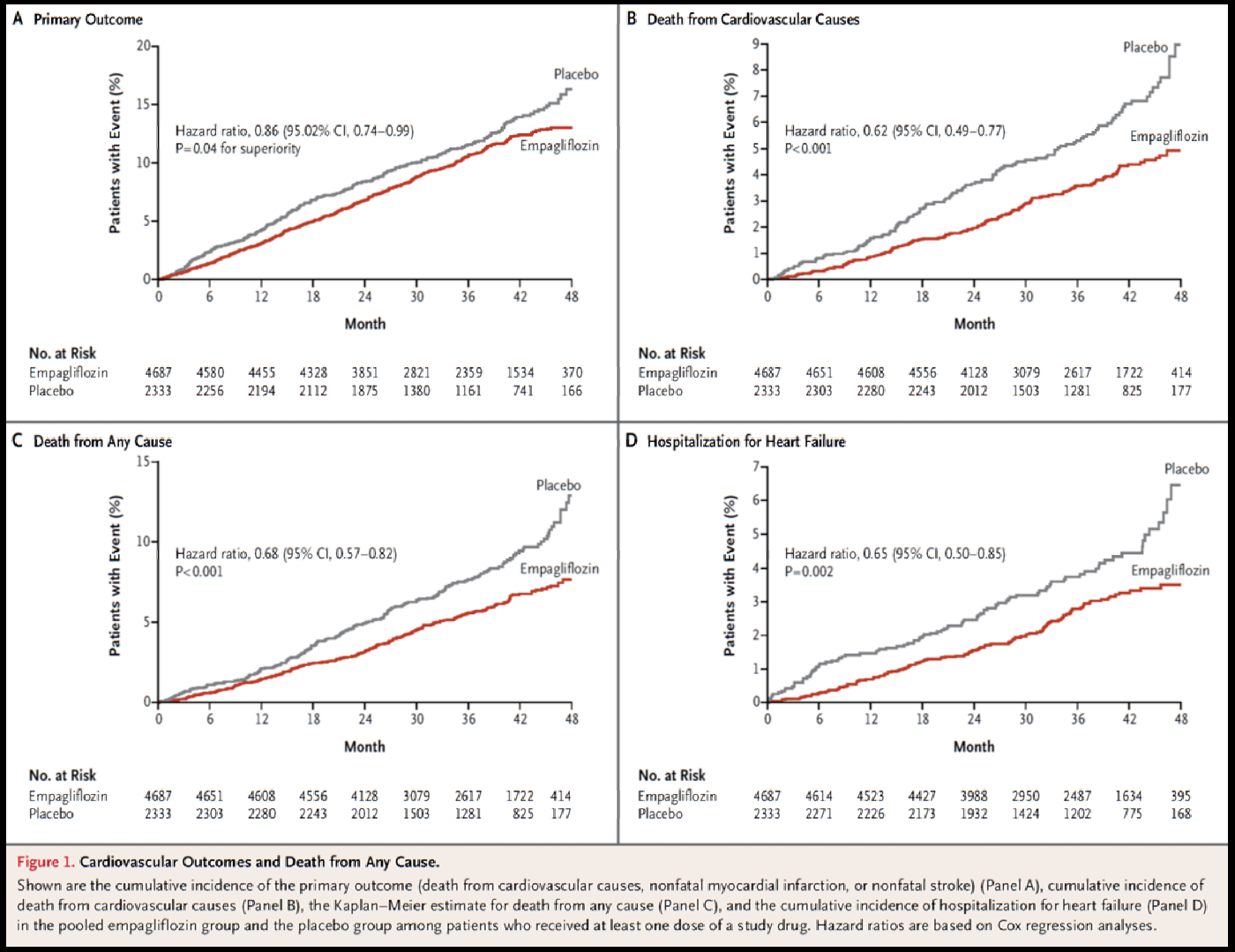


Figure 1. Cardiovascular Outcomes and Death from Any Cause.
Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

Zinman et al. 2015. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes New Engl J Med 373:2117-2128

EMPA-REG OUTCOME Mortality Study



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EMPA-REG OUTCOME Mortality Study

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78–1.01)	
Noninferiority						<0.001†
Superiority						0.08†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57–0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

Zinman et al. 2015. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes New Engl J Med 373:2117-2128

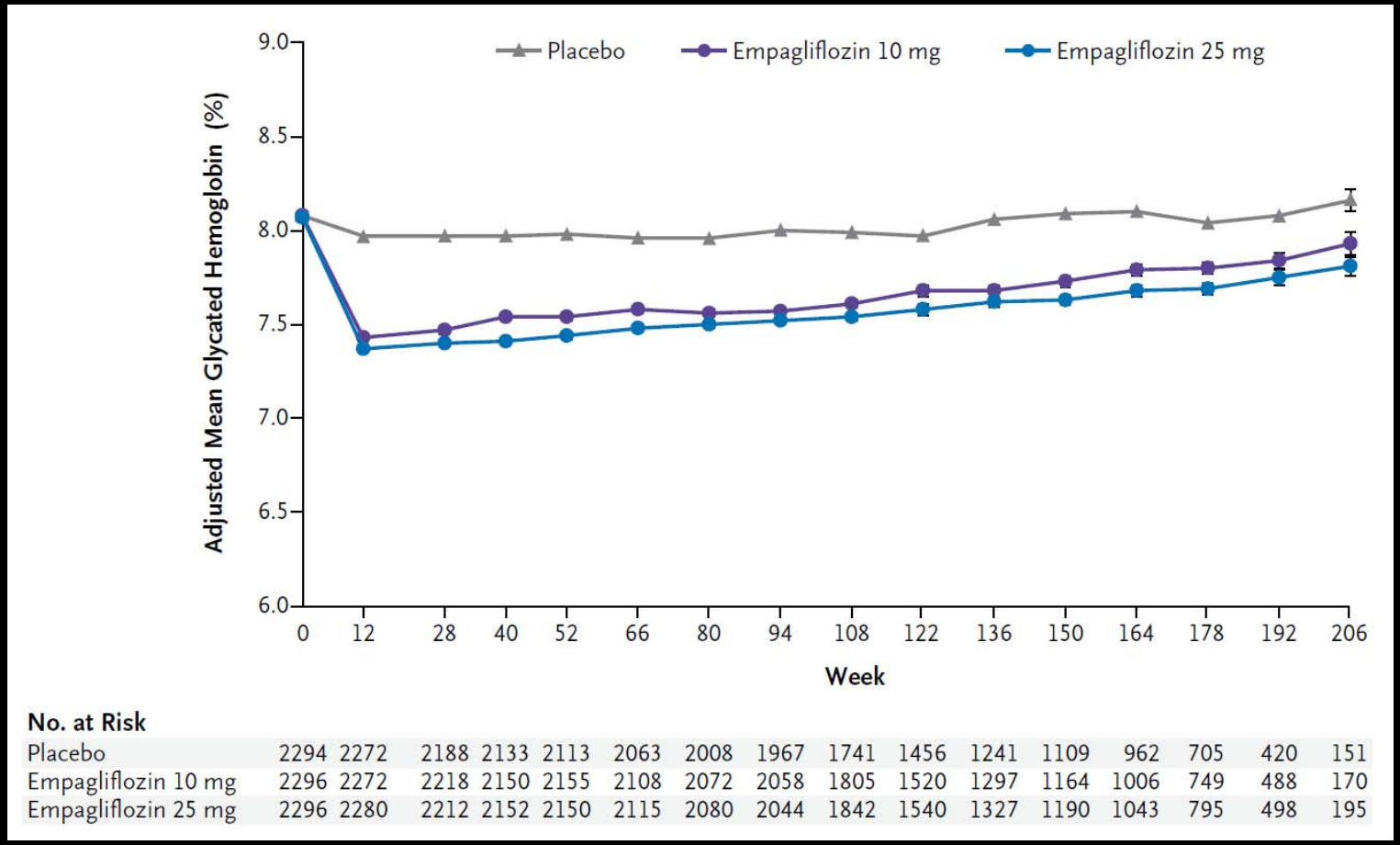
EMPA-REG OUTCOME Mortality Study

Table 2. Adverse Events.*

Event	Placebo (N = 2333)	Empagliflozin, 10 mg (N = 2345)	Empagliflozin, 25 mg (N = 2342)	Pooled Empagliflozin (N = 4687)
	number of patients (percent)			
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event§§	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture‖‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

Zinman et al. 2015. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes New Engl J Med 373:2117-2128

EMPA-REG OUTCOME – It's not glycemia



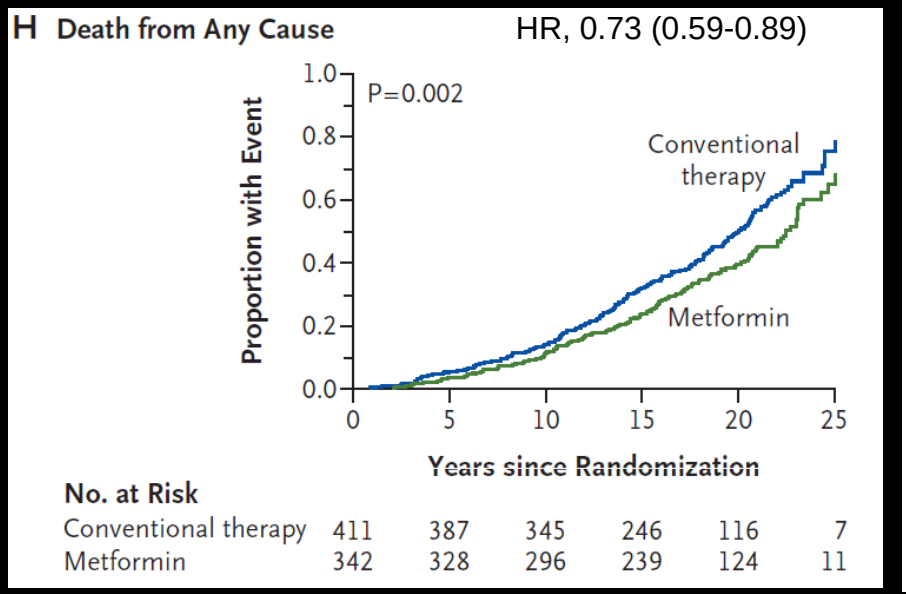
No. at Risk

Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

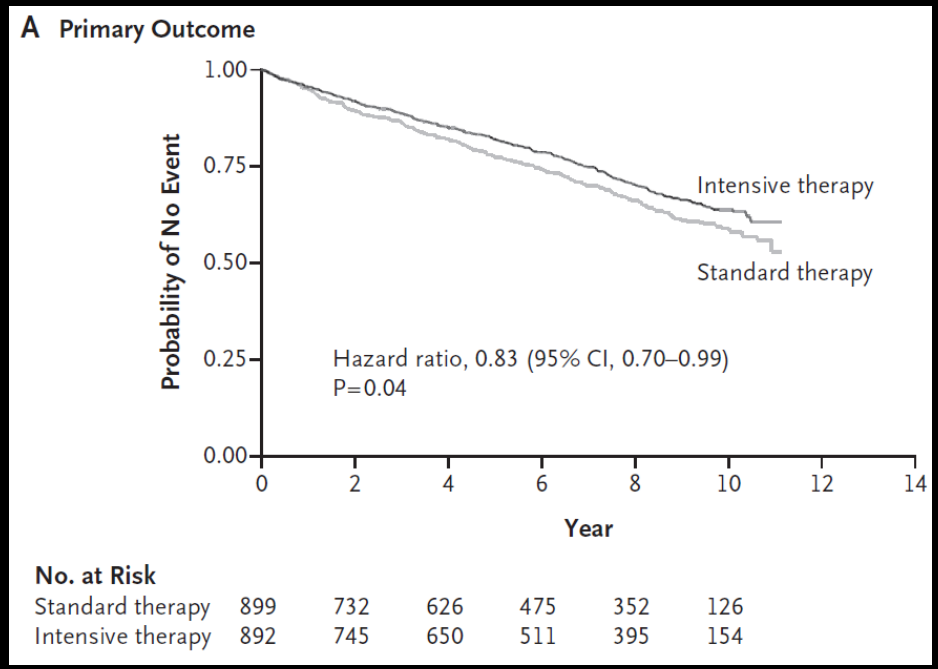
Zinman et al. 2015. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes New Engl J Med 373:2117-2128

Mortality Perspective—Intensive Glycemic Control Takes A Long Time to Matter in Type 2 Diabetes

UKPDS

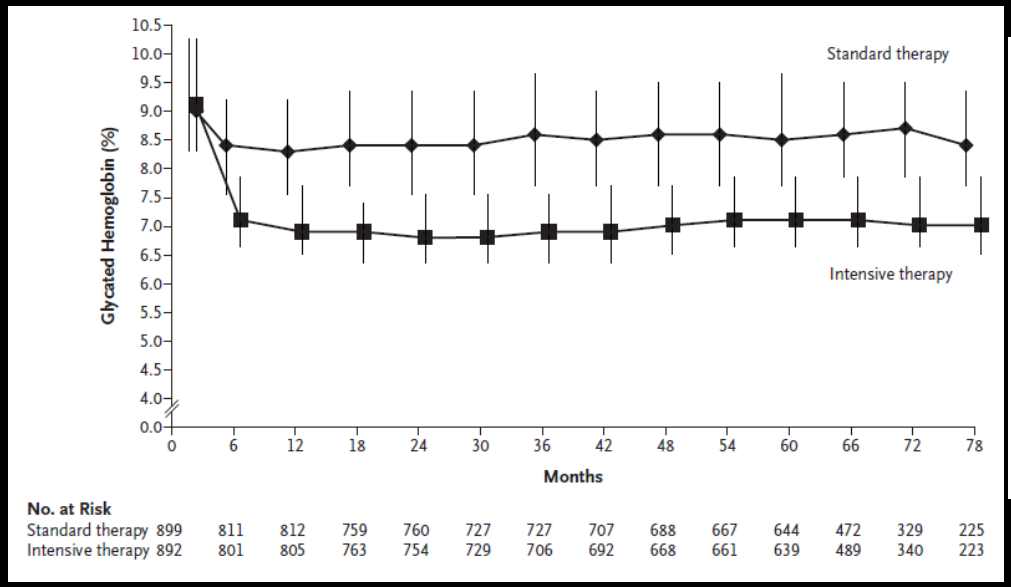


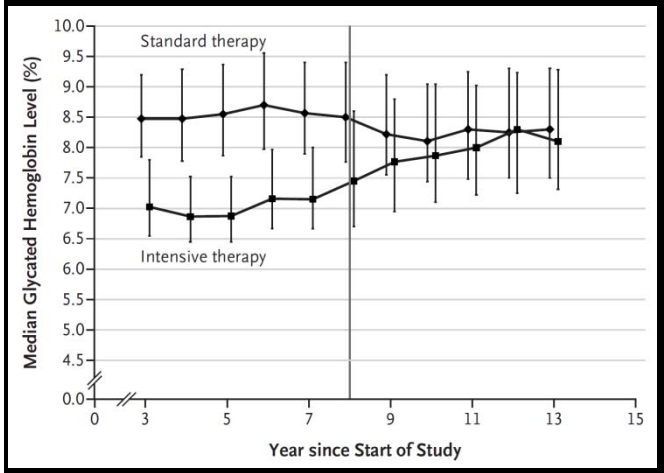
VADT



Holman et al. 2008. 10-year follow-up of intensive glucose control in type 2 diabetes. New Engl J Med. 359:1577-89 .
Hayward et al. 2015. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. New Engl J Med. 372: 2197-2206.

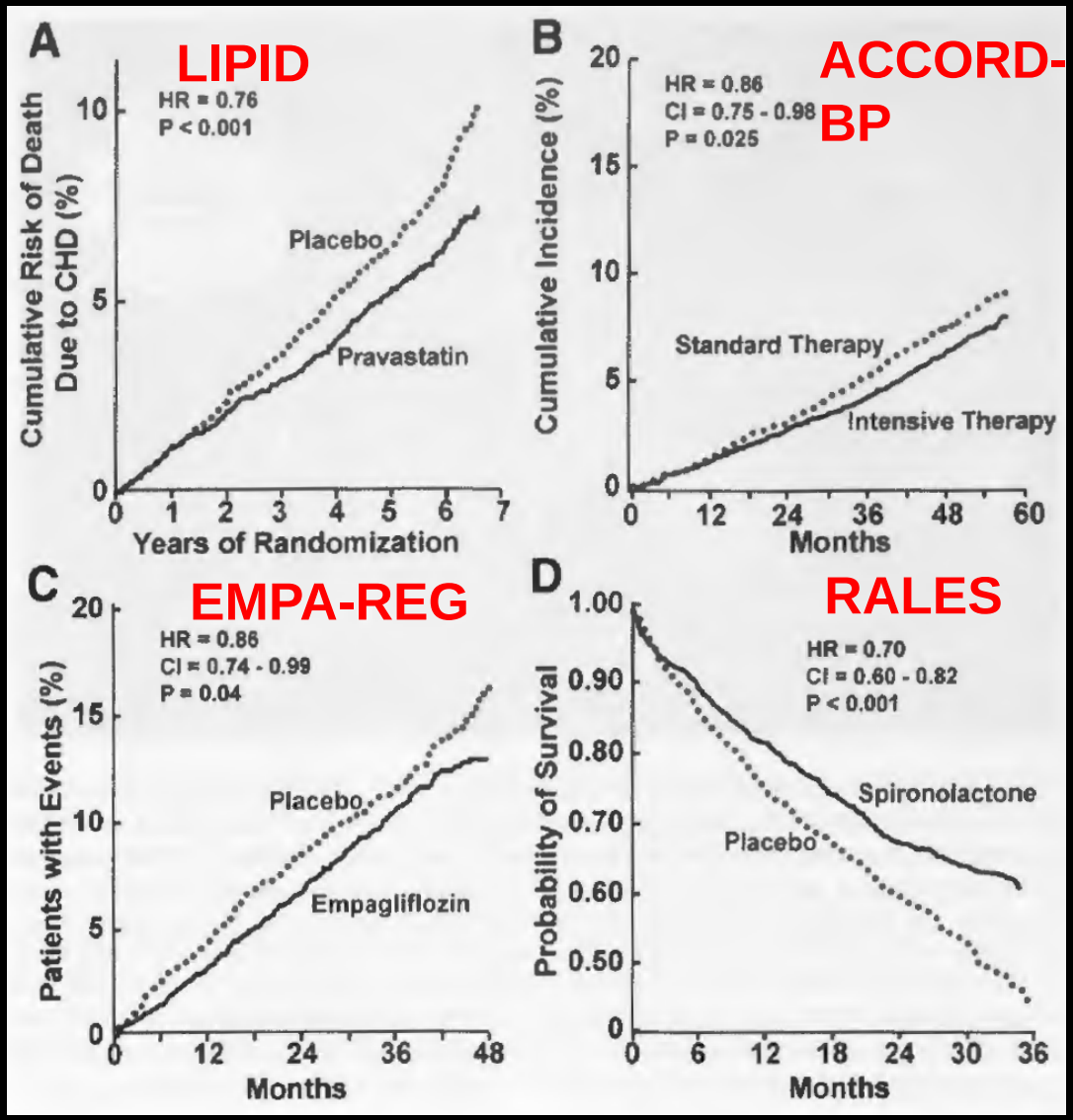
Metabolic Memory in VADT





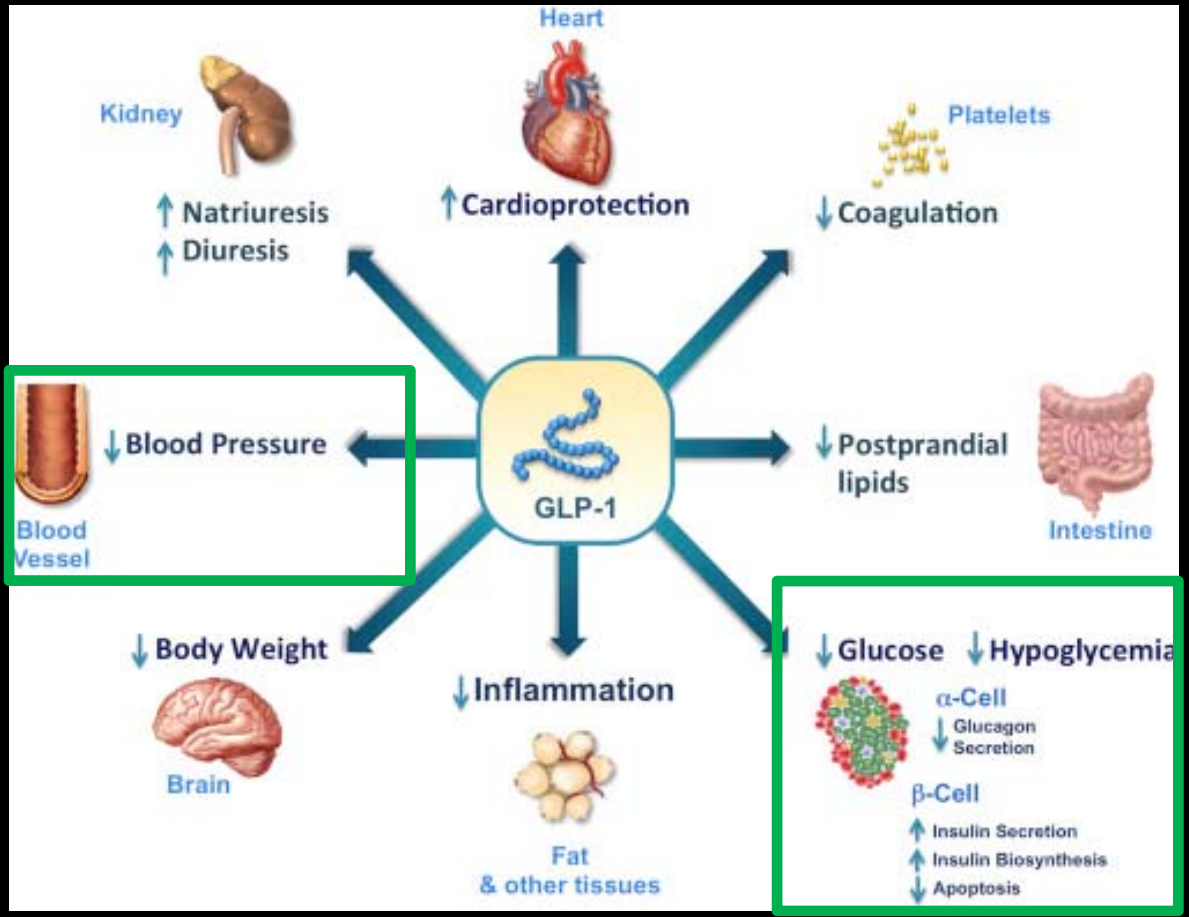
Duckworth et al. 2009. Glucose control and vascular complications in veterans with type 2 diabetes. New Engl J Med. 360:129-39
Hayward et al. 2015. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. New Engl J Med. 372: 2197-2206.

Pace of Effect: Blood Pressure Control Is King



Abdul-Ghani et al. 2016. SGLT2 Inhibitors and Cardiovascular Risk: Lessons Learned from the EMPA-REG OUTCOME Study. Diabetes Care. 39:717-725.

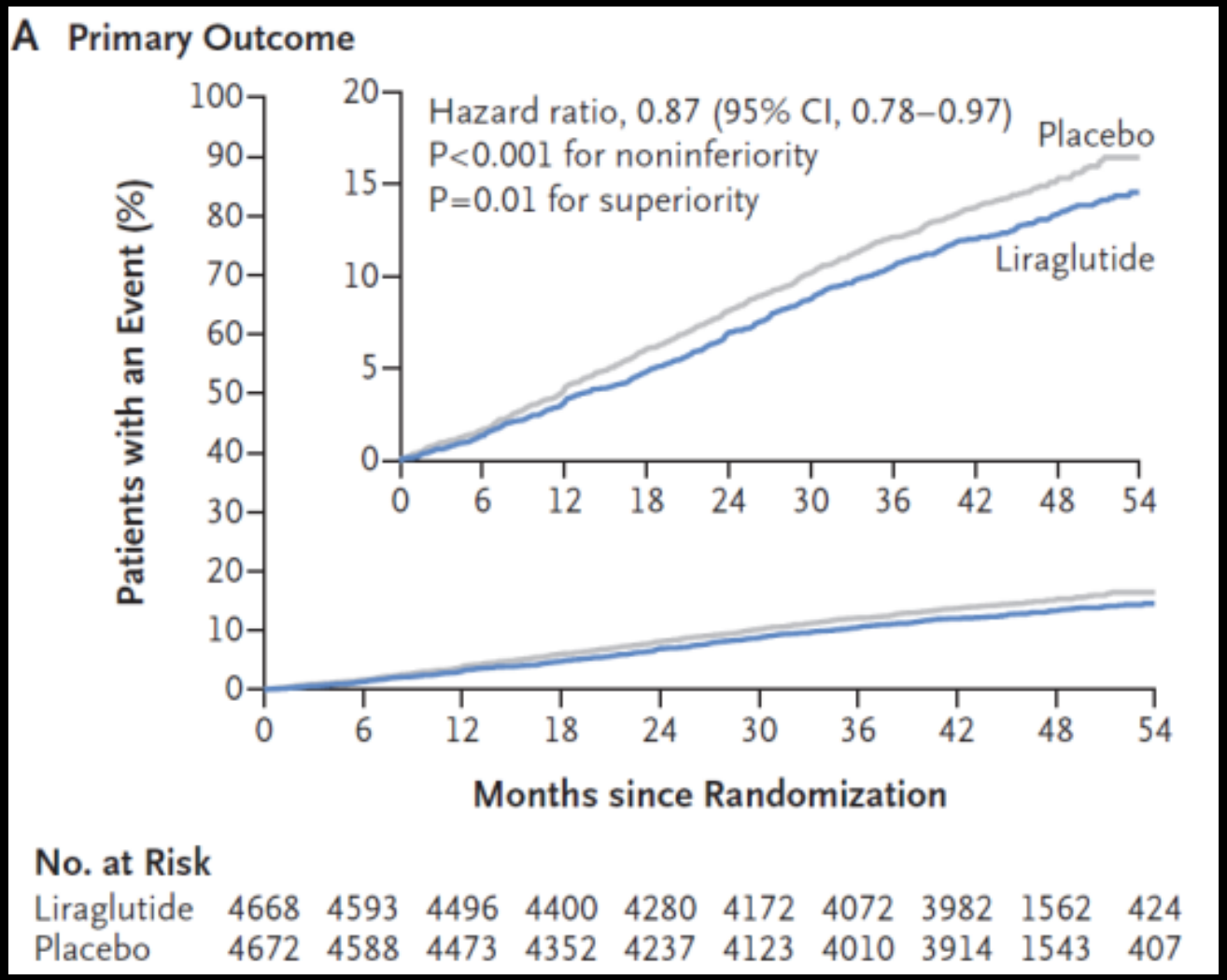
GLP-1 Interlude



Drucker DJ. 2016. The Cardiovascular Biology of Glucagon-like Peptide-1 Cell Metabolism 24:15-30.

Exenatide (Extendin-4) is a Gila Monster Salivary Venom GLP-1 Agonist

Liraglutide Lowers BP, too (LEADER)



Marso et al. 2016 Liraglutide and cardiovascular outcomes in type 2 diabetes. New Engl J Med. 375: 311-322.

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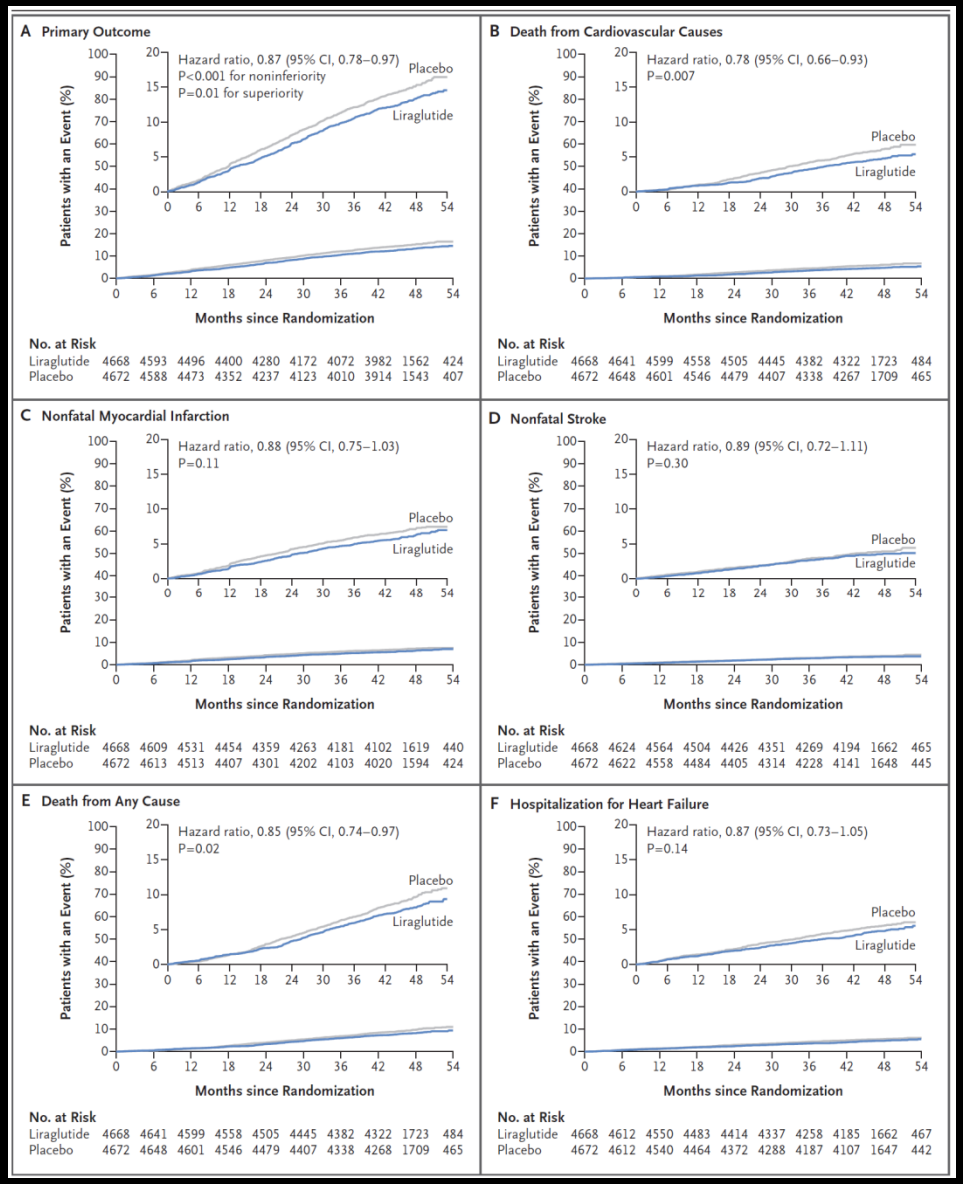


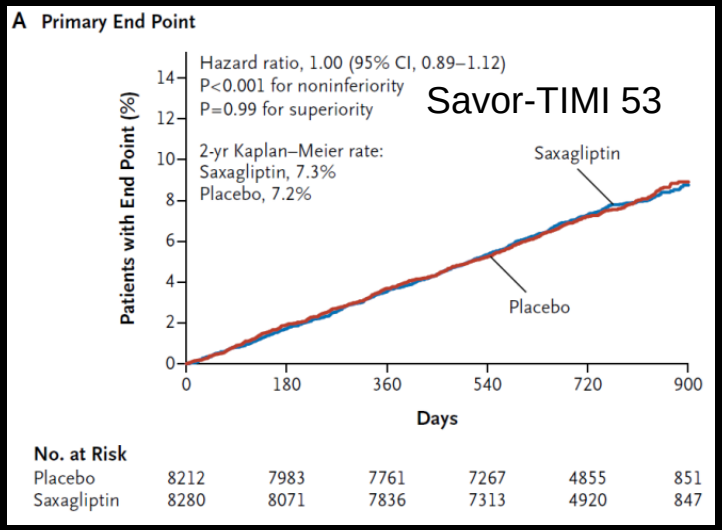
Marso et al. 2016 Liraglutide and cardiovascular outcomes in type 2 diabetes. New Engl J Med. 375: 311-322.

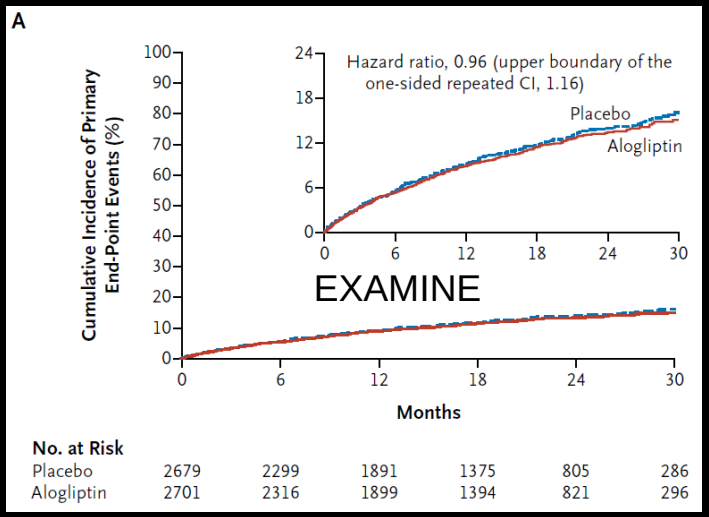
Other GLP1 Agonist Trials In the Works

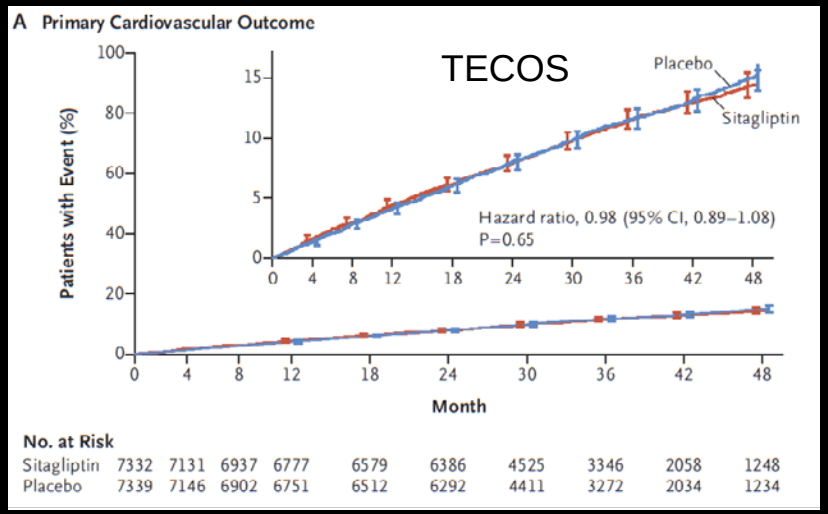
Drug	Trial, n	Duration and Inclusion	Primary Outcome
Exenatide QR (2 mg weekly)	EXSCEL n = 14,000	June 2010-April 2018; History of 0-3 oral antihyperglycemic agents; insulin alone or with 2 oral drugs A1c 6.5 to 10% Age ≥ 18 years	Time to first CV event in the primary composite of CV death, nonfatal MI or nonfatal stroke
Liraglutide (1.2 and 1.8 mg OD)	LEADER n = 9,340	August 2010-November 2015 Known CV, cerebrovascular or peripheral vascular disease or chronic renal failure or chronic heart failure A1c ≥ 7% Age ≥ 50 years	Time to first event included in the composite of CV death, MI or ischemic stroke
Lixisenatide (10 and 20 mcg daily)	ELIXA. n = 6,000	June 2010 to Feb 2015 Minimum 2 years follow-up Spontaneous ACS admitted in last 180 days A1c 5.5 to 11% Age ≥ 30 years	Composite for CV death, nonfatal MI, nonfatal stroke or hospitalization for unstable angina
Dulaglutide (0.75 and 1.5 mg weekly)	REWIND n = 9,622	July 2011 to April 2019; median 3.1 years Age ≥ 50 years with established clinical vascular disease Age ≥ 55 years and subclinical vascular disease Age ≥ 60 years and at least 2 CV risk factors A1c ≤ 9.5%	Time to first event included in the composite of CV death, MI or ischemic stroke

Modified from Wilding, Rajeev and DeFronzo 2016. Positioning SGLT2 Inhibitors/Incretin-based therapies in the treatment algorithm. Diabetes Care. 39:S154-164.

DPP4 Inhibitors Are Safe, But not Magical







Linagliptin: CAROLINA 6,000 subjects; CARMELINA 8,3000 subjects

Scirica et al. 2013. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. New Engl J Med. 369:1317-26.
White et al. 2013. Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes New Engl J Med. 369:1327-35.
Green et al. 2015. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. New Engl J Med 373:232-242.

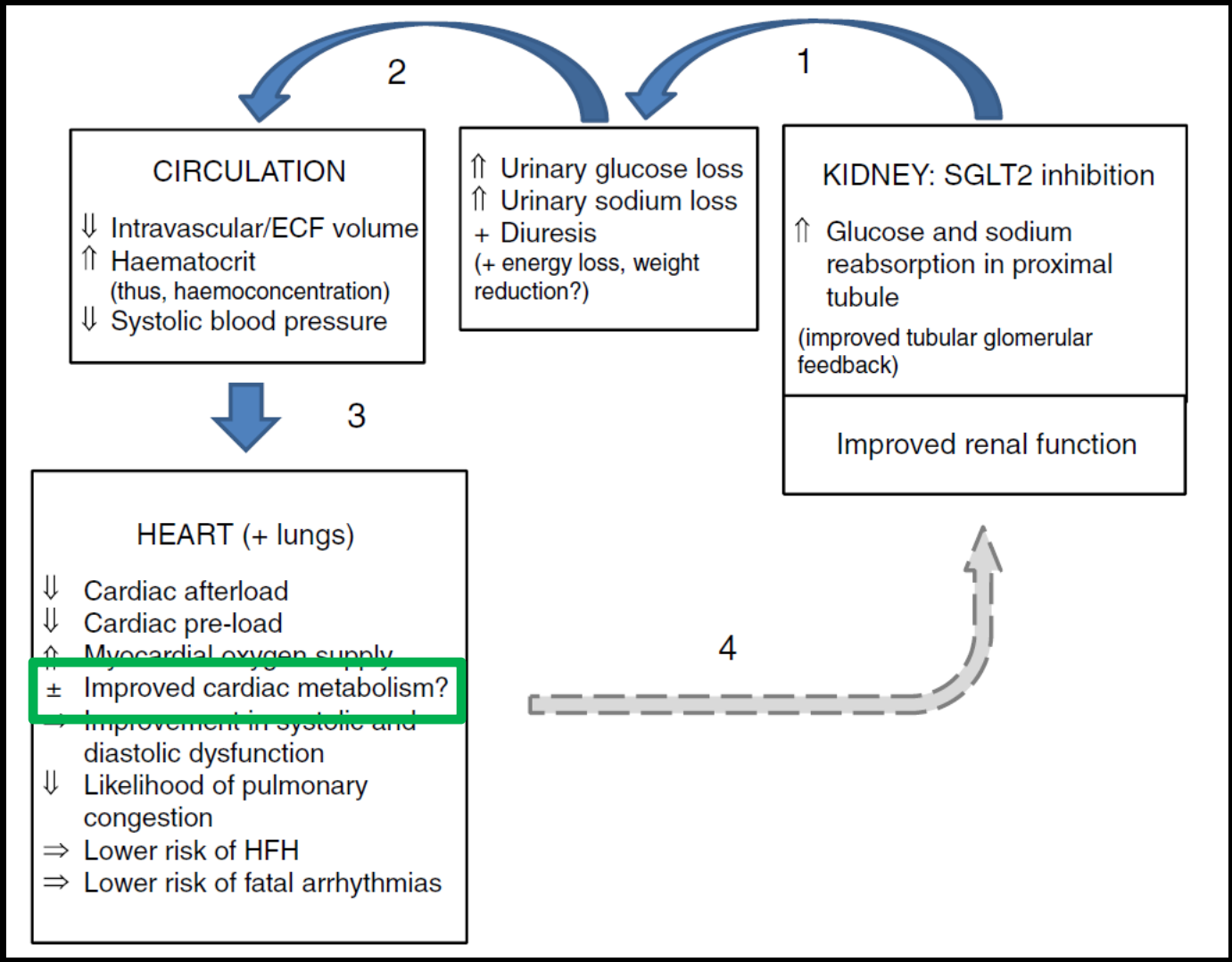
Are SGLT2 Inhibitors All About Blood Pressure?

Table 1—Possible mechanisms that could contribute to the reduction of CV mortality by empagliflozin in the EMPA-REG OUTCOME study

Effect	Likelihood	Reason
Metabolic actions		
Lowered plasma glucose concentration	Unlikely	Hyperglycemia is a weak CV risk factor; benefit of HbA_{1c} reduction on CVD takes ~10 years to observe
Increased fax oxidation	Unlikely	Increased oxygen demand per ATP generated
Increased plasma ketone concentration	Unlikely	Increased oxygen demand per ATP generated
Increased plasma uric acid concentration	Unlikely	Causal association with CVD not established
Increased plasma glucagon concentration	Unlikely	Physiological increase in glucagon has no effect on CV function
Weight loss	Unlikely	Weight loss is modest but may contribute to long-term reduction in blood pressure
Change in plasma electrolyte concentration	Unlikely	No consistent changes observed
Hemodynamic actions		
Decrease in blood pressure	Likely	Rapid reduction in blood pressure correlates with early CV benefit; proven CV protection in prior studies
Diuretic effect and decrease in extracellular fluid volume	Likely	Rapid reduction in extracellular fluid volume correlates with early CV benefit; proven protection against CHF in prior studies
Impaired arterial elasticity	Possible	Arterial stiffness is a CV risk factor; empagliflozin reduces arterial stiffness
Direct effect on the myocardium	Unlikely	No evidence
Decreased sympathetic tone	Possible	No increase in heart rate despite decrease in blood pressure and extracellular fluid volume

Abdul-Ghani et al. 2016. SGLT2 Inhibitors and Cardiovascular Risk: Lessons Learned from the EMPA-REG OUTCOME Study. Diabetes Care. 39:717-725.

Are SGLT2 Inhibitors All About Blood Pressure?



Sattar et al. 2016. SGLT2 Inhibition and Cardiovascular Events: why did EMPA- REG Outcomes Surprise and what are the likely mechanisms. Diabetalogia. 59:1333-1339.

Or Is It the “Super-Fuel” Ketones?

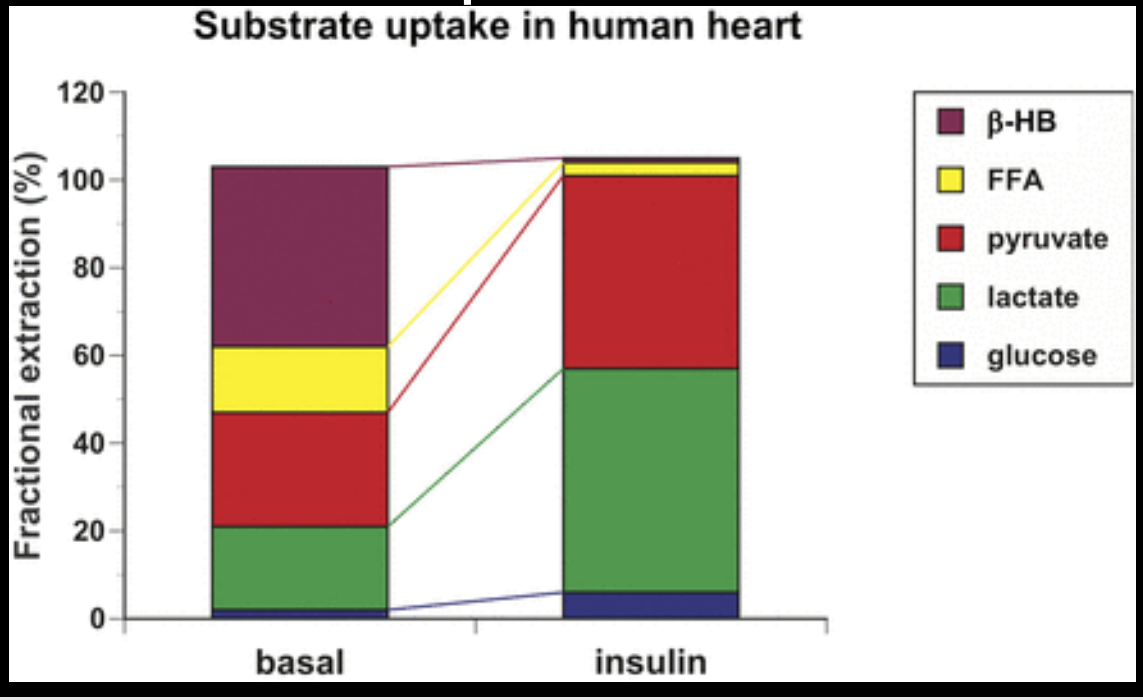


Table 1—Comparative mitochondrial energetics of β-hydroxybutyrate oxidation

	Glucose	Palmitate	Pyruvate	β-HB
O_2 used (L/mol)	134	515	56	101
Heat of combustion (kcal/mol)	670	2,385	279	487
O_2 cost of calorie (mL/kcal)	200	216	201	207
Heat of combustion per C_2 (kcal/mol)¶	224	298	186	244

In terms of oxygen (O_2) cost, the energy yield of β-HB oxidation is comparable to those of glucose and pyruvate, and lower than that of palmitate. If the energy yield is calculated per C_2 unit, β-HB oxidation is superior to glucose and far better than palmitate. β-HB, β-hydroxybutyrate.
¶According to Sato et al. (41).

Ferrannini et al. 2016. CV Protection in the EMPA-REG OUTCOME Trial: A “Thrifty Substrate” Hypothesis. Diabetes Care. 39:1108-1114.

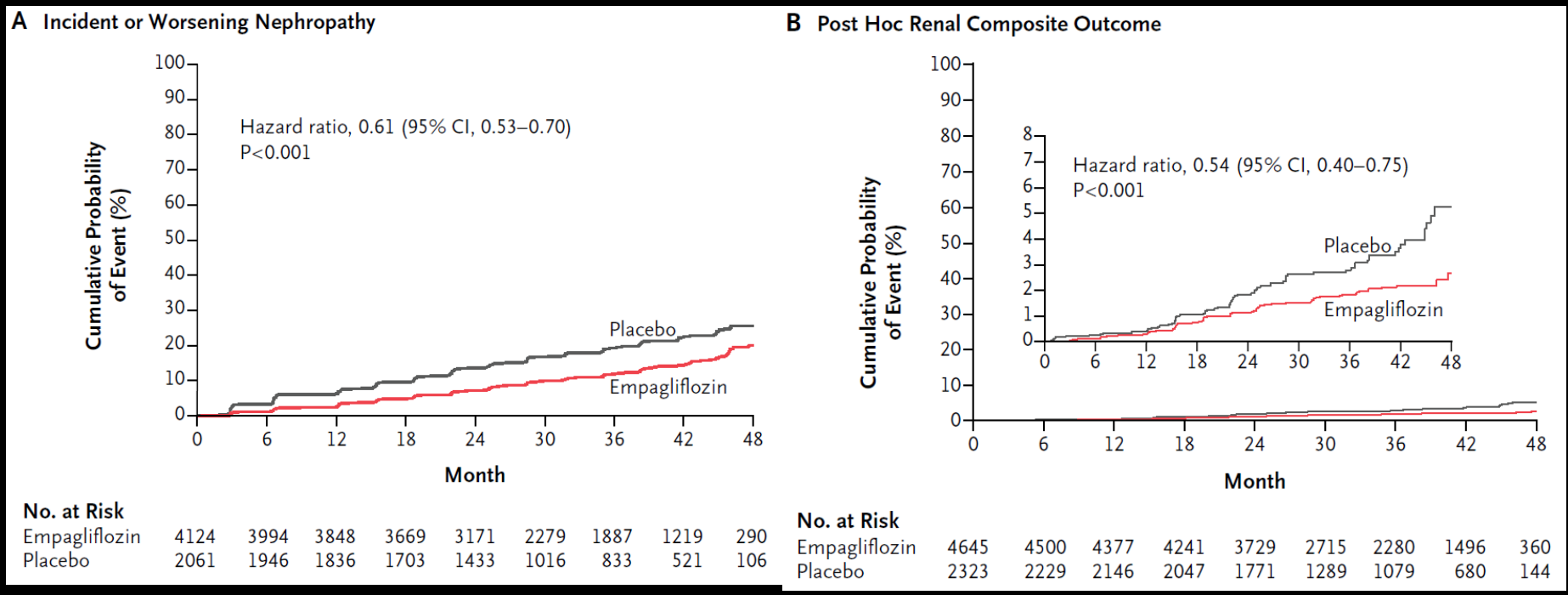
EMPA-REG OUTCOME Renal Study

Table 1. Characteristics of the Patients at Baseline, According to the Estimated Glomerular Filtration Rate (eGFR).*

Characteristic	Patients with eGFR of 59 ml per Minute per 1.73 m^2 or Less		Patients with eGFR of 60 ml per Minute per 1.73 m^2 or More	
	Placebo (N=607)	Empagliflozin (N=1212)	Placebo (N=1726)	Empagliflozin (N=3473)
Age — yr	67.1±8.2	67.1±7.6	61.9±8.6	61.7±8.5
Male sex — no. (%)	418 (68.9)	816 (67.3)	1262 (73.1)	2518 (72.5)
Body-mass index†	30.9±5.4	31.0±5.5	30.6±5.2	30.5±5.2
Glycated hemoglobin — %‡	8.03±0.85	8.07±0.86	8.10±0.84	8.07±0.84
Interval of >10 yr since diagnosis of type 2 diabetes — no. (%)	422 (69.5)	794 (65.5)	917 (53.1)	1876 (54.0)
Blood pressure — mm Hg				
Systolic	136.4±18.7	136.1±18.0	135.6±16.7	135.0±16.6
Diastolic	74.6±10.3	74.5±9.9	77.6±10.0	77.4±9.5
Estimated glomerular filtration rate — ml/min/1.73 m^2	48.6±7.8	48.4±8.2	82.7±16.6	83.1±17.1
Urinary albumin-to-creatinine ratio — no. (%)§				
<30	283 (46.6)	566 (46.7)	1099 (63.7)	2223 (64.0)
30 to 300	205 (33.8)	411 (33.9)	470 (27.2)	926 (26.7)
>300	115 (18.9)	223 (18.4)	145 (8.4)	286 (8.2)
Cholesterol — mg/dl				
Low-density lipoprotein¶	85.0±36.1	84.4±35.8	84.8±35.1	86.5±36.0
High-density lipoprotein‖	42.9±10.7	44.2±12.5	44.4±11.5	44.7±11.7
Triglycerides — mg/dl‖	180.4±107.4	173.5±108.1	167.2±125.6	169.4±136.4
Coronary artery disease	482 (79.4)	938 (77.4)	1281 (74.2)	2606 (75.0)
History of stroke**	156 (25.7)	293 (24.2)	397 (23.0)	791 (22.8)
Peripheral artery disease††	130 (21.4)	314 (25.9)	349 (20.2)	667 (19.2)
Cardiac failure‡‡	89 (14.7)	174 (14.4)	155 (9.0)	288 (8.3)
Concomitant medication — no. (%)				
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	502 (82.7)	1031 (85.1)	1366 (79.1)	2766 (79.6)
Beta-blocker	415 (68.4)	829 (68.4)	1083 (62.7)	2226 (64.1)
Diuretic	355 (58.5)	710 (58.6)	633 (36.7)	1336 (38.5)
Calcium-channel blocker	227 (37.4)	446 (36.8)	561 (32.5)	1082 (31.2)
Statin	461 (75.9)	966 (79.7)	1312 (76.0)	2663 (76.7)
Aspirin	495 (81.5)	981 (80.9)	1432 (83.0)	2894 (83.3)
Metformin	369 (60.8)	711 (58.7)	1365 (79.1)	2746 (79.1)
Sulfonylurea	234 (38.6)	480 (39.6)	758 (43.9)	1534 (44.2)
Insulin	357 (58.8)	699 (57.7)	778 (45.1)	1551 (44.7)

Wanner et al. 2016. Empagliflozin and progression of kidney disease in type 2 diabetes New Engl J Med 2016. 375:323-334.

EMPA-REG OUTCOME Renal Study



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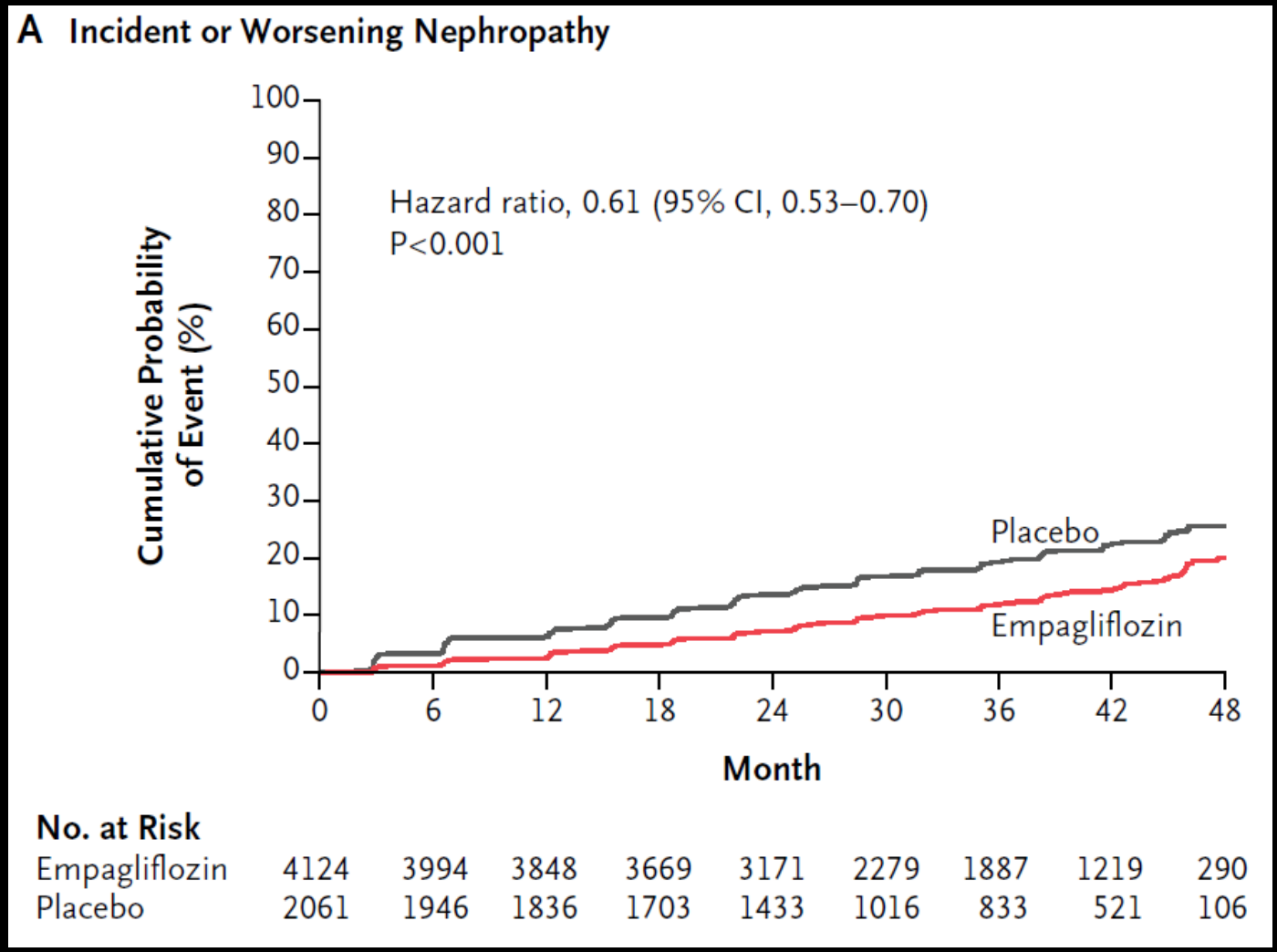
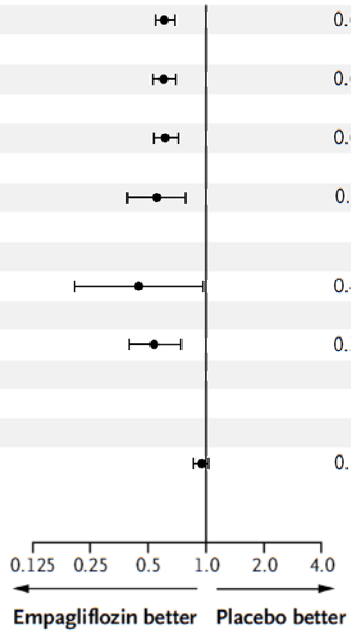


Wanner et al. 2016. Empagliflozin and progression of kidney disease in type 2 diabetes. New Engl J Med 2016. 375:323-334.

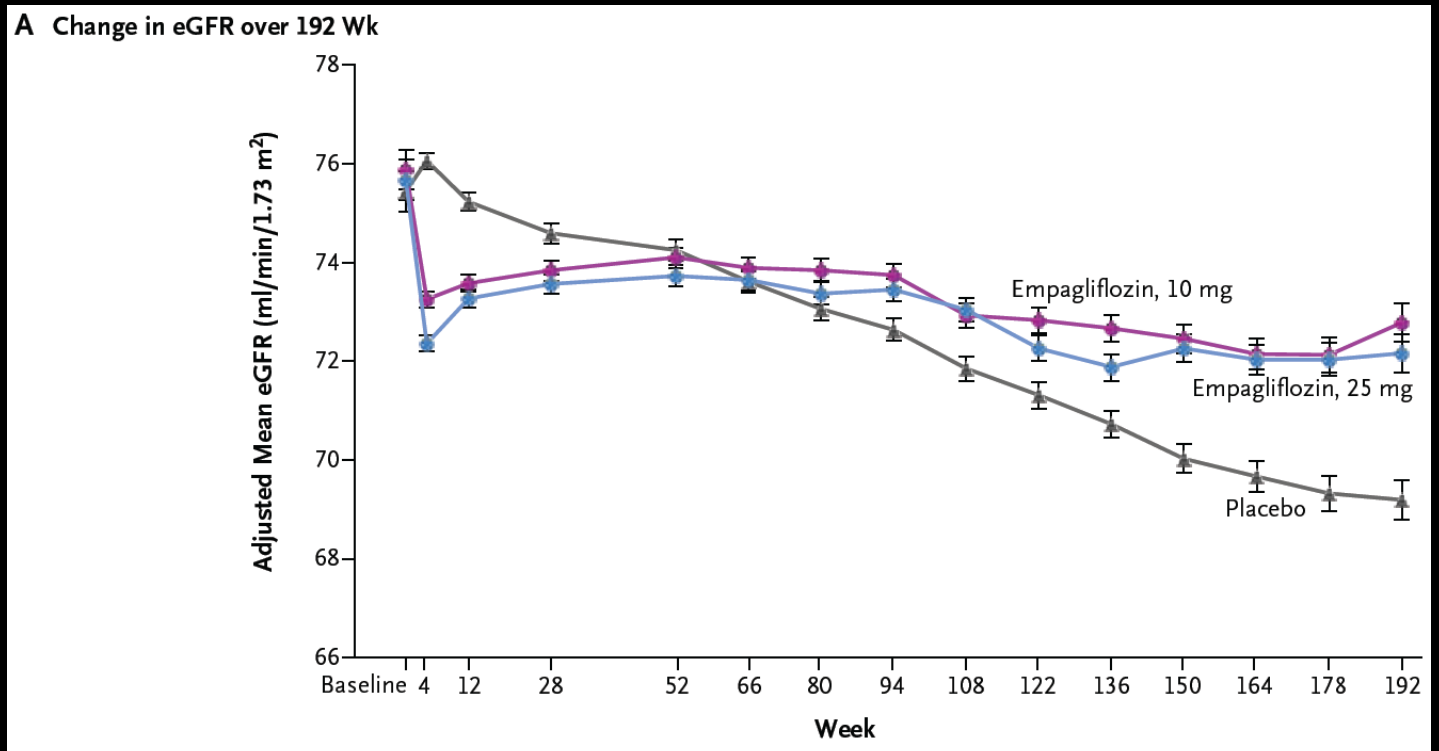
EMPA-REG OUTCOME Renal Study

Renal Outcome Measure	Empagliflozin: no. with event/ no. analyzed (%)	Empagliflozin: rate/1000 patient-yr	Placebo: no. with event/ no. analyzed (%)	Placebo: rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m²	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



Wanner et al. 2016. Empagliflozin and progression of kidney disease in type 2 diabetes. New Engl J Med 2016. 375:323-334.

EMPA-REG OUTCOME Renal Study



No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

Wanner et al. 2016. Empagliflozin and progression of kidney disease in type 2 diabetes. New Engl J Med 2016. 375:323-334.

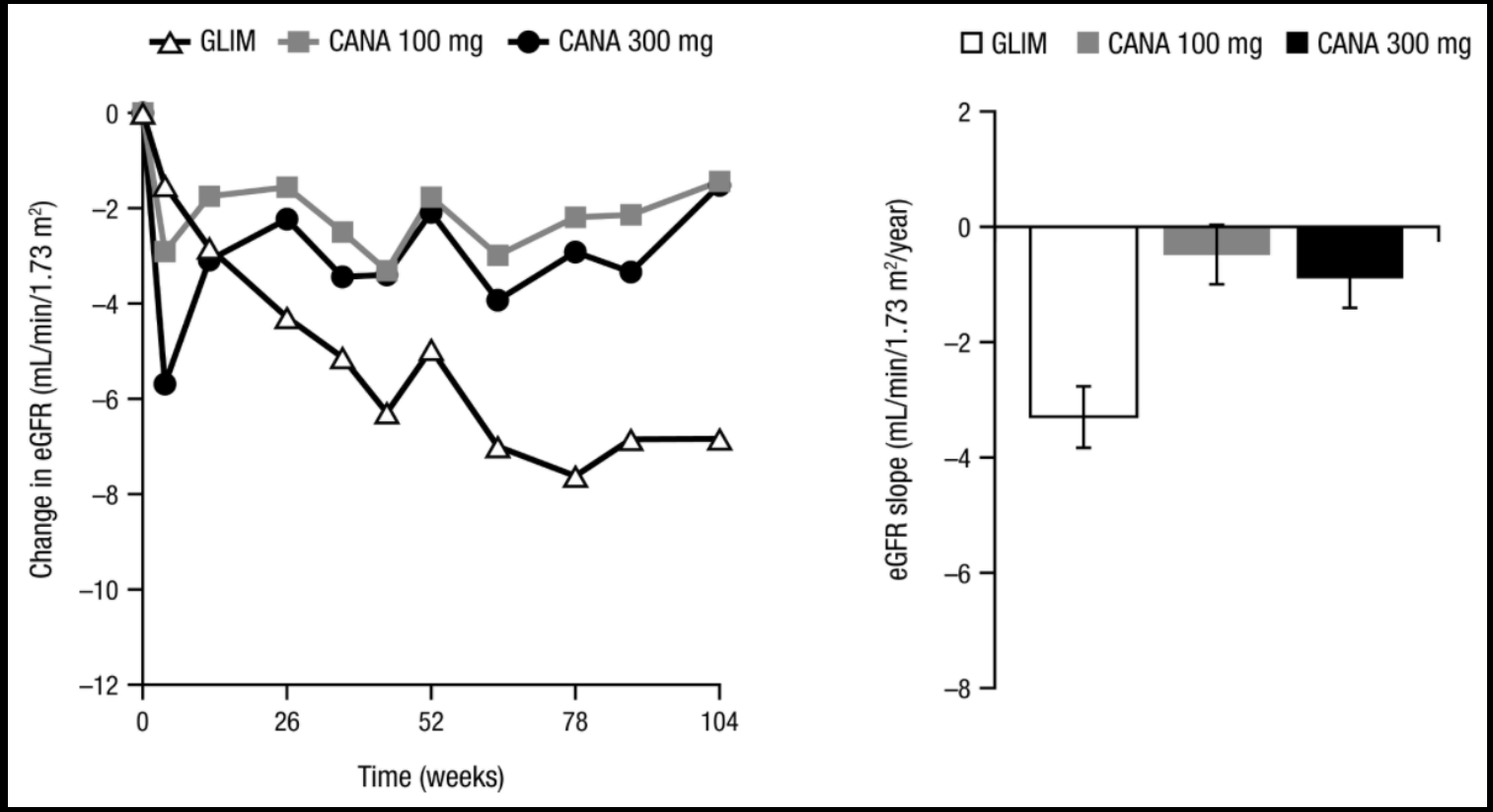
All SGLT2 Inhibitors In

Drug	Trial, n	Duration and Inclusion	Primary Outcome
Canagliflozin	CANVAS, n = 4,411	Dec 2009-April 2017; History of high risk for CV disease A1c 7 to 10.5% Age ≥ 30 years	MACEs: CV death, nonfatal MI and non-fatal stroke
Dapagliflozin	DECLARE- TIMI 58 n = 17,150	April 2013-April 2019 High risk for CV events with DM2 Age ≥ 40 years	Time to first event included in the composite of CV death, MI or ischemic stroke
Empagliflozin	EMPA-REG OUTCOME. N = 7,034	July 2010 to April 2015; median 3.1 years High CV risk A1c 7 to 10% Age ≥ 18 years	Composite of CV death, nonfatal MI or nonfatal stroke

CV, cardiovascular; MACE, major cardiac adverse events; MI, myocardial infarction

Modified from Wilding, Rajeev and DeFronzo 2016. Positioning SGLT2 Inhibitors/Incretin-based therapies in the treatment algorithm. Diabetes Care. 39:S154-164.

CANVAS Interim Report



Heerspink et al. Canagliflozin (CANA) slows progression of renal function decline independent of of glycemic effects. Oral Presentation. American Diabetes Association Meeting. June 11, 2016 .

Outline

1. Case
2. Physiology of Renal Glucose Handling
3. SGLT-2 Pharmacology
4. Trials, including GLP-1 agonist and DDP4I comparisons
5. Speculation on Mechanisms
6. Back to case
7. Framework for polypharmacy

Case

Four months later, the patient reported a 5 kg weight loss. His morning blood glucose was consistently below 150 mg/dL.

He states that his primary care physician discontinued nifedipine, decreased the chlorthalidone to 12.5 mg daily, and decreased the lisinopril dose to 30 mg daily because his home and ambulatory blood pressure readings showed a 5 mm Hg drop to an average of 127 mm Hg systolic (he had experienced a 7 mm Hg drop after starting exenatide, 4 months prior).

The Hemoglobin A1c after this visit was 7.1%. Review of his glucometer readings showed no hypoglycemic episodes.

Outline

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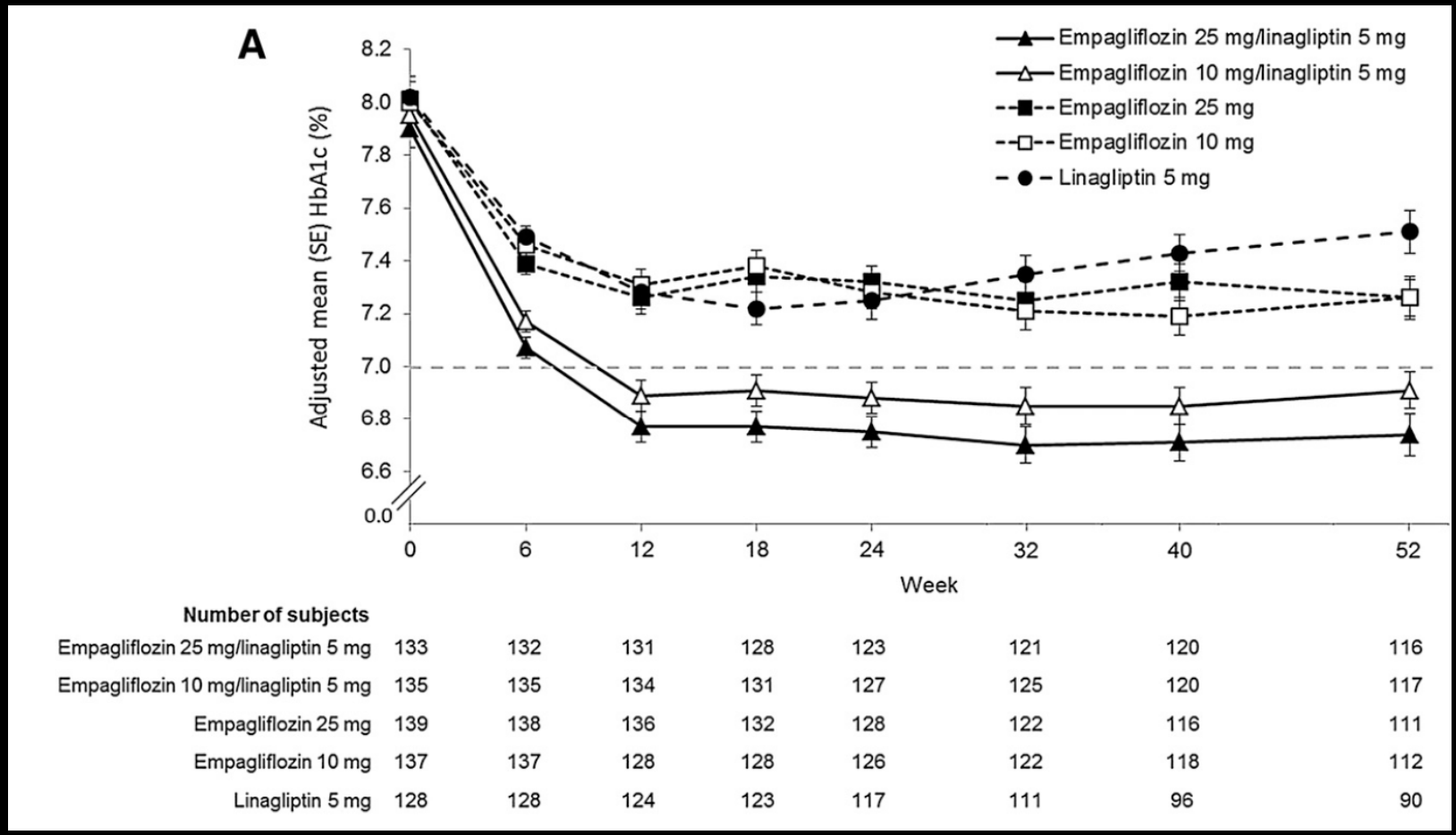
Empagliflozin-Linagliptin Synergy

On a bed of Metformin



Number of subjects								
Empagliflozin 25 mg/linagliptin 5 mg	133	132	131	128	123	121	120	116
Empagliflozin 10 mg/linagliptin 5 mg	135	135	134	131	127	125	120	117
Empagliflozin 25 mg	139	138	136	132	128	122	116	111
Empagliflozin 10 mg	137	137	128	128	126	122	118	112
Linagliptin 5 mg	128	128	124	123	117	111	96	90

DeFronzo et al. 2015 Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 38:384-93. Erratum 1173.

When?

Summary and Conclusions

Incretin-based therapies and SGLT2 inhibitors are relatively new treatments for T2DM but have become well established in clinical use. Because of their attributes (efficacy in reducing HbA_{1c}, weight loss, blood pressure reduction, low propensity to cause hypoglycemia, good safety profile, improvement in CV outcomes with empagliflozin, and correction of multiple pathophysiological abnormalities present in T2DM), we believe that these agents should be used early in the natural history of T2DM. Their ultimate place in guidelines will be strongly influenced by the results of ongoing CV and renal outcome trials, novel combination studies, and considerations of comparative efficacy and cost compared with older, "more established," but less effective agents when long-term durability of glycemic control is considered.

Internal medicine is the "pluripotent stem cell" of specialties. That being said, let's face it: Tweaking diabetic drugs is boring, but the opportunity to craft a career that suits your interests, personality, and lifestyle at the different phases of your life is priceless.

Wilding, Rajeev and DeFronzo 2016. Positioning SGLT2 Inhibitors/Incretin-based therapies in the treatment algorithm Diabetes Care. 39:S154-164.
http://www.kevinmd.com/blog/2016/08/dont-love-specialty-heres.html